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Clinical Reasoning: A 70-year-old woman with acute-onset weakness and progressive hemiataxia

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SECTION 1

A 70-year-old woman with a history of insulin-dependent type 2 diabetes mellitus (IDDM), breast cancer treated with lumpectomy in 2012, hyperlipidemia, hypertension, coronary artery disease, and congestive heart failure with pacemaker presented with acute-onset difficulty using her right arm and leg. She was in her usual state of health until 3 weeks before admission, when she tripped over her grandson's toy on the floor, falling on her right side. Prior to falling, neither she nor her family had noted any weakness or difficulty with walking. Because her symptoms failed to improve over 3 weeks, she eventually presented to an emergency department.

There, her examination was notable for occasional mumbling speech but no dysarthria or aphasia. She had intact memory, cranial nerves, and sensation. There was moderate right arm and leg weakness (MRC [Medical Research Council] grade 4/5). She was unsteady on standing and was unable to walk independently. Labs were notable for hemoglobin A_{1c} 10.3, low-density lipoprotein 78.

Questions for consideration:

1. What is the localization of this lesion?
2. What is the initial differential diagnosis?

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SECTION 2

Based on the history and examination, physicians at the outside hospital were concerned for a left subcortical stroke, so she underwent head CT. Although this showed extensive white matter disease, there was no visible acute stroke. To obtain an MRI with her cardiac pacemaker, she was transferred to our tertiary care academic center.

On admission to our hospital, she was noted to have right-sided moderate dysmetria of arm and leg, as well as mild right-sided weakness. There were no areas of restricted diffusion on brain MRI, ruling out acute to subacute stroke (gadolinium was not administered). The cerebellum and brainstem were unremarkable. However, there were extensive periventricular and subcortical white matter T2/fluid-attenuated inversion recovery hyperintensities concerning for chronic small vessel disease.

Her neurologic status progressively worsened over several days. She became oriented only to person and place (not to date), with poor recall. Oculomotor testing revealed slow pursuits with catch-up saccades and corrective saccades on vestibuloocular reflex testing. She developed mild left-sided dysmetria of the arm and leg, in addition to her right-sided moderate dysmetria, dyssynergia, and dysdiadochokinesia. She required assistance from 2 people to stand because of axial ataxia. Motor, reflex, and sensory examination remained unchanged.

Questions for consideration:

1. How do the MRI and new examination findings change the differential diagnosis?
2. What studies would help determine the diagnosis?

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SECTION 3

The deterioration of this patient's balance and coordination, as well as development of encephalopathy, indicated a progressive, global process (see table 1 for differential diagnosis).

The patient initially declined lumbar puncture. Extensive laboratory and investigative workup was notable for an elevated erythrocyte sedimentation rate (38), low vitamin B_{12} (215) and thiamine (44), and the presence of anti-thyroid peroxidase antibody (478) and anti-gastric parietal cell antibodies. Otherwise, the following studies were within normal limits: thyroid-stimulating hormone, free T4, anti-Ro, anti-La, ANCA (anti-neutrophil cytoplasmic antibodies) panel, anti-nuclear antibody, rheumatoid factor, C3, C4, lyme serology, antiphospholipid antibodies, Whipple serology, celiac panel, serum immunoglobulin E, vitamin E, copper, methylmalonic acid, and homocysteine. The patient also underwent cancer screening to evaluate the possibility of a paraneoplastic process with mammogram, PET brain/body, and thyroid ultrasound for a small lesion that did not require biopsy. She was repleted with high-dose IV thiamine and intramuscular cyanocobalamin without clinical improvement.

Several weeks after admission, her serum anti-glutamic acid decarboxylase 65 (anti-GAD_{65}) antibodies were found to be elevated at 13,720 U/mL (normal ≤1 U/mL). Based on this result, we were concerned that her cerebellar ataxia might be due to an anti-GAD–associated neurologic disorder. She also had IDDM, pernicious anemia, and thyroiditis, all of which can be associated with anti-GAD_{65} antibodies.

Questions for consideration:

1. Which tests confirm an anti-GAD_{65} antibody–associated neurologic disorder?
2. Is there a threshold level of serum anti-GAD_{65} antibodies that causes neurologic disease?

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Table 1 Differential diagnosis for subacute cerebellar ataxia with encephalopathy

Category	Specific diseases
Ischemia	Multifocal strokes, recrudescence of prior stroke, vasculitis
Autoimmune	Demyelinating diseases, celiac disease, Miller Fisher syndrome, anti-GAD_{65}–associated
Malignancy	Paraneoplastic (anti-Hu/Yo), ependymoma, metastasis
Neurodegenerative	Multiple system atrophy, Creutzfeldt-Jacob disease
Genetic	Spinocerebellar ataxia, Wilson disease
Infectious	VZV, EBV, PML, Whipple disease, Lyme disease
Nutrition	Vitamin B_1/B_{12}/E deficiency, chronic alcohol abuse
Trauma	Postconcussive syndrome
Toxins/medications	Alcohol, heavy metals, toluene, phencyclidine, anti-epileptic medications, lithium, barbiturates, amiodarone

Abbreviations: EBV = Epstein-Barr virus; GAD_{65} = glutamic acid decarboxylase 65; PML = progressive multifocal leukoencephalopathy; VZV = varicella-zoster virus.

SECTION 4

The patient agreed to a lumbar puncture 2 weeks into her hospital course revealing white blood count 3, protein 39, and intrathecal synthesis of oligoclonal bands, with a positive anti-GAD_{65} antibody at 54.2 nmol/L (normal ≤0.02 nmol/L). Based on these findings, she was diagnosed with anti-GAD_{65} antibody–associated cerebellar ataxia.

For first-line therapy, she was treated with plasmapheresis (table 2).[1,2] Her chronic kidney disease, multiple vascular risk factors, and religious preferences made her a poor candidate for IV immunoglobulin, and IDDM was a relative contraindication for steroids.[3,4] She received 4 of 5 planned plasmapheresis sessions because of development of severe anemia. Her examination did not improve over the course of plasmapheresis. For long-term immunomodulatory therapy, she was started on anti-CD20 B cell therapy (rituximab).[5] Unfortunately, she was lost to follow-up after 3 months.

DISCUSSION This is a unique case of anti-GAD_{65} cerebellar ataxia presenting with acute-onset hemiataxia. Symptom onset for this condition is typically gradual over months to years. Despite her acute presentation, which prompted a stroke evaluation, our patient continued to worsen over several days. This, and the normal MRI, prompted further workup.

Our patient has many typical features of patients reported with anti-GAD_{65} antibody–associated neurologic disorders, including sex (80%–90% are female), age (mean age at diagnosis is 59 years), IDDM (50%–60% of patients), and autoimmune thyroid disorder (85% have organ-specific autoimmune disorders). In addition, her gait ataxia was

Table 2 Literature review of treatment and response in anti-GAD_{65}–associated cerebellar ataxia

Ref.	No. of patients	Average age at onset, y	Treatment/response
e1	20[a]	58	3: IVMP or IVIg alone, all improved mRS by 1–2 points; 7: IVIg or IVMP then chronic IVIg, 1 improved; 6: IVIg then immunosuppression, 3 improved, 2 stabilized, 1 worsened; 3: steroids then immunosuppression with transient improvement in 2; 1: PLEX, IVIg, and oral steroids without improvement
e2	7[b]	57	3: IVMP then mycophenolate mofetil with dramatic improvement; 1: IVMP alone with dramatic improvement; 1: IVMP then maintenance steroids with dramatic improvement; 2: IVIg then cyclophosphamide or IVIg with dramatic improvement
e3	3	70	2: IVIg then Rituxan with some improvement and stability; 1: IVIg, Rituxan, Cytoxan with continued deterioration
e4	4	54	Monthly IVMP: mild/no improvement
e5	2	62	IVIg: very mild improvement
e6	2	71	PLEX followed by rituximab: sustained improvement in function but persistent disability
e7	1	56	IVMP followed by PLEX, changed to mycophenolate mofetil with intermittent IVMP with gradual improvement but persistent deficits
e8	1	70	IVMP with temporary improvement, then IVIg without effect, then azathioprine with clinical stabilization
e9	1	34	IVMP followed by IVIg: marked improvement leading to full recovery
e10	1	50	IVIg: marked improvement and stabilization leaving some deficits
e11	1	66	Oral steroids: mild improvement in cerebellar symptoms
e12	1	72	IVIg: no improvement
e13	1	58	IVMP followed by oral taper, then azathioprine: marked improvement in cerebellar symptoms
e14	1	38	IVMP monthly: modest clinical improvement over 6 mo
e15	1	66	IVMP with transient improvement then IVIg with some improvement
e16	1	63	PLEX with temporary improvement, followed by IVIg without improvement
e17	1	47	IVIg: slight improvement in ataxia
e18	1	76	IVMP then oral steroid taper with dramatic improvement
e19	1	42	Oral prednisone and azathioprine: almost complete improvement in cerebellar symptoms
e20	1	62	IVIg: no improvement

Abbreviations: GAD_{65} = glutamic acid decarboxylase 65; IVIg = IV immunoglobulin; IVMP = IV methylprednisolone; mRS = modified Rankin Scale; PLEX = plasma exchange; Ref. = reference.
[a] Thirty-four patients were described in the study but only the 20 who were treated are included here.
[b] Forty-one patients in the study were GAD_{65}+, only 7 had strong response to treatment, and only these had their treatment courses listed; the other 34 are not included in this table.

disproportionate to her limb ataxia, similar to what has been described.[6,7] It is important to note that 12% to 22% of patients diagnosed with anti-GAD_{65}–associated cerebellar ataxia have an underlying malignancy, necessitating evaluation for neoplasm.[6,8]

Antibodies against GAD have been associated with a variety of systemic and neurologic conditions including type 1 diabetes mellitus, polyendocrine autoimmunity, stiff-person syndrome (classic and variant), pure cerebellar ataxia, limbic encephalitis, progressive encephalomyelitis with rigidity and myoclonus, palatal tremor, and refractory epilepsy. The serum level of anti-GAD_{65} antibody may be useful for distinguishing whether neurologic disease is related to anti-GAD_{65} antibody. IDDM is associated with relatively low levels (10–1,000 U/mL), and levels greater than approximately 2,000 U/mL appear to be more specific for neurologic disorders associated with GAD_{65} or polyendocrine autoimmunity.[9,10] Specificity for neurologic disease can be improved by evaluating for intrathecal synthesis and oligoclonal bands in the CSF, necessitating a lumbar puncture in suspected cases for accurate diagnosis.[4]

Given the rarity of anti-GAD_{65}–associated cerebellar ataxia, treatment is not well defined. The most common first-line treatments are IV immunoglobulin, methylprednisolone, and plasma exchange, often followed by repeat courses or long-term immunosuppression with rituximab, mycophenolate mofetil, or azathioprine (table 2). Unfortunately, this condition is often resistant to treatment. Recent case series have demonstrated sustained response rates of 17% to 35%.[6,8] Poor or inadequate treatment response may be attributable to several factors, including (1) underrecognition resulting in delayed treatment, (2) delay in aggressive treatments until after cerebellar atrophy is already present, and (3) differing target epitopes of the anti-GAD_{65} antibody. Whether starting treatment before evidence of cerebellar atrophy prevents damage remains to be shown.

Anti-GAD_{65}–associated cerebellar ataxia is an uncommon immune-mediated disorder that, to our knowledge, has never been described as presenting with acute-onset hemiataxia. This case emphasizes the importance of maintaining a broad differential diagnosis when initial workup is inconclusive. It also highlights the key presenting features of anti-GAD_{65}–associated cerebellar ataxia and the importance of screening and monitoring over time for an underlying malignancy given its relatively high frequency.

AUTHOR CONTRIBUTIONS

Karisa Schreck conceptualized the study, analyzed the data, and drafted the manuscript. Jennifer Orthmann-Murphy analyzed the data and drafted the manuscript. Scott Newsome conceptualized the study and revised the manuscript.

ACKNOWLEDGMENT

The authors thank Dr. Argye Hillis for her work conceptualizing this case.

STUDY FUNDING

No targeted funding reported.

DISCLOSURE

K. Schreck and J. Orthmann-Murphy report no disclosures relevant to the manuscript. S. Newsome has received consultant fees for scientific advisory boards from Biogen, Genzyme, and Novartis and has received research funding from Biogen, Novartis, and the National MS Society. Go to Neurology.org for full disclosures.

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Neurology 2016;87;e264-e268
DOI 10.1212/WNL.0000000000003377